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Associations between Supper Timing and Mortality from Cardiovascular Disease among People with and without Hypertension

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Aim: Less is known about the impact of supper time on cardiovascular disease (CVD) risk among hypertensives and nonhypertensives. We aimed to explore this issue in a cohort study.

Methods: We analyzed the data of 72,658 participants (15,386 hypertensives and 57,272 nonhypertensives) aged 40–79 years without a history of CVD at baseline (1988–1990) under the Japan Collaborative Cohort study. Supper time was assessed based on self-reported questionnaires categorized as before 17:00, between 17:00 and 20:00, after 20:00, irregular supper time, and reference supper time (17:00–20:00). Hazard ratios (HRs) and 95% confidence intervals (95% CI) of CVD mortality were calculated according to supper time after adjustment for potential confounders, stratified by hypertensive status and age group (<65 and ≥ 65 years).

Results: During a median of 19.4 years of follow-up, 4,850 CVD deaths were recorded. Compared with the reference time, the risk of CVD mortality was higher for irregular supper time for the total population, either hypertensives or nonhypertensives, more specifically hypertensives aged ≥ 65 years; the multivariable HR (95% CI) of CVD mortality in the total population was 1.28 (1.11–1.50, $P<0.01$). The supper time of $>20{:}00$ tended to be associated with the higher risk only for hypertensives; the multivariable HR was 1.39 (0.98–1.96, $P=0.06$).

Conclusion: Irregular supper time was associated with an increased risk of CVD mortality. Supper timing could be a surrogate marker for CVD risk.

Key words: Supper timing, Hypertension, Cardiovascular disease, Cohort study

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. There were 17.8 million deaths from CVD globally in 2017, which accounted for approximately 32% of the total deaths[1)]. A history of hypertension is associated with a greater risk of CVD incidence and mortality[2, 3)], and the number of patients with hypertension aged 30–79 years has increased worldwide from 317 million men and 331 million women in 1990 to 652 and 626 million, respectively, in 2019[4)]. New evidence for hypertension management is required to reduce the risk of CVD mortality.

Several previous studies have shown associations between meal timing and the risk of CVD. A 2.7-year follow-up for the database of approximately 1.9 million Japanese employees showed that the number

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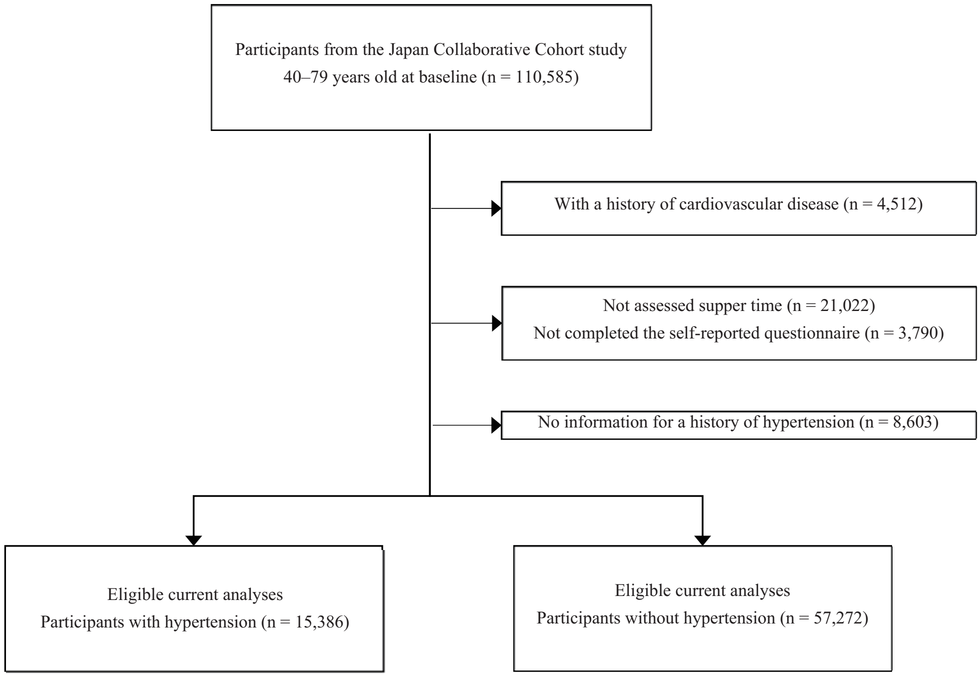

Fig. 1. Flowchart of current analyses

of unhealthy eating behaviors of skipping breakfast, late-night dinner, and bedtime snacking (0, 1, 2, and 3) was weakly associated with higher risks of myocardial infarction, angina pectoris, stroke, and heart failure[5)]. A 19.2-year follow-up of the Japan Collaborative Cohort (JACC) study of 28,625 men and 43,213 women aged 40–79 years reported that irregular supper time was associated with a higher risk of hemorrhagic stroke among the general population[6)]. Meal timing has been recognized as a key factor in the enhancement of oxidative stress and the development of hypertension, especially among older adults[7, 8)]. However, no studies have focused on the association between meal timing and the risk of CVD among hypertensives and nonhypertensives.

Aims

The present study aimed to explore the specific association between supper timing and the risk of CVD mortality in patients with hypertension, using a nationwide prospective cohort in Japan.

Methods

Study Population

We used data from the JACC study. The details of the JACC study have been described elsewhere[9, 10)]. In brief, the study included a total of 110,585 participants (46,395 men and 64,190 women) aged 40–79 years, living in 45 areas throughout Japan from 1988 to 1990 (the baseline). In the current analysis, we excluded 4,512 participants owing to a history of CVD. Additionally, we excluded participants 1) who did not assess supper time (n=21,022, 11 areas), 2) with incomplete self-report questionnaires (n=3,790), and 3) with missing data on the history of hypertension (n=8,603). Therefore, 72,658 participants were included in the recent study. All the participants were stratified according to history of hypertension (n=15,386) or no history of hypertension (n=57,272) **(Fig. 1)**. The definition of the history of hypertension was assessed using a self-reported questionnaire. The validity was assessed with mean systolic/diastolic blood pressure (SBP/DBP) for 28% of the total population (n=20,389) and the prevalence of anti-hypertensive medication users (n=10,635), which accounted for 15% of the total population. The mean SBP/DBP values were 147/86 mmHg among people with a history of hypertension (n=3,934) and 127/77 mmHg among people without a history of hypertension (n=16,455). The prevalence of anti-hypertensive medication was 69.0% in those with hypertension and 0% in those without hypertension. Informed consent was obtained from all participants or community leaders. This study was approved by the Ethics Committee of the Graduate School of Medicine, Nagoya University, and Osaka

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University.

Mortality Surveillance

For mortality surveillance in each community, the investigators conducted a systematic review of death certificates, all of which were forwarded to the public health center in the area of residence. Mortality data were sent centrally to the Ministry of Health and Welfare, and the causes of death were coded according to the 10th revision of the International Classification of Diseases (ICD-10) for the National Vital Statistics. The Family Registration Law in Japan requires the registration of death. Therefore, all deaths that occurred in the cohort were ascertained by referring to death certificates from a public health center, except for those of participants who died after they had moved from their original community, in which case such participants were censored. The final follow-up was completed at the end of 2009, and CVD mortality was determined using ICD-10 codes I01–I99.

Baseline Survey

Demographic characteristics, medical history, and lifestyle factors were assessed using a self-report questionnaire. The information for supper time was obtained based on a self-report questionnaire. We asked the participants, "When do you eat dinner time regularly?". A single-choice answer was as follows: before 17:00, between 17:00 and 20:00, after 20:00, and irregular supper time.

Statistical Approaches

Mean values, standard derivation, and proportions of baseline characteristics were calculated according to supper time <17:00, 17:00–20:00, >20:00, or irregular supper time. Significant differences were examined using analyses of variance. Cox proportional hazards were used to examine age- and sex-adjusted hazard ratios (HRs), multivariable-adjusted HRs, and 95% confidence intervals (95% CIs) of CVD mortality according to the supper time. We referenced the group at 17:00–20:00. The multivariable HRs were adjusted for potential confounders, including age; sex; body mass index (<18.5, 18.5–24.9, and ≥ 25.0 kg/m^2); never-smoker (yes or no); history of hypertension (yes and no); history of diabetes (yes and no); sleep duration (<5.5, 5.5–6.4, 6.5–7.4, 7.5–8.4, and 8.5–12.0 h/day); educational level (≤ 18 and ≥ 19 years); marital status (currently married or not); and occupational status (office worker or others). When values were missing, we imputed the dummy variables. Furthermore, we examined stratified analyses by history of hypertension and age group (<65 and ≥ 65 years). The interaction was examined using cross-product terms of supper timing, history of hypertension, and age group. All statistical analyses were performed using SAS version 9.4 (SAS Institute Japan, Ltd., Japan). All reported *P*-values were two-sided, and the significance level was set at $P<0.05$.

Results

The mean age at baseline was 57.0 years, and 41.6% of the population was composed of men. Over a median of 19.4 years of follow-up, 4,850 participants died from CVD (1,955 with hypertension and 2,895 without hypertension).

Table 1 shows the baseline characteristics according to supper time. Compared with people with a supper time of 17:00–20:00, those with supper time >20:00 and with irregular supper time were more likely to be younger, men, overweight, current or past smokers, more educated, office workers, married, less hypertensive, and to have a sleep duration of 5.5–7.4 h/day. People with a supper time of <17:00 showed the opposite trends for the above characteristics. Trends for the baseline characteristics according to supper time were similar between hypertensives and nonhypertensives **(Supplemental Table 1)**.

The association between supper timing and the risk of mortality from CVD is shown in **Table 2**. Irregular supper time was associated with a higher risk of CVD mortality than a supper time of 17:00–20:00; the multivariable HR (95% CI) was 1.28 (1.11–1.49, $P<0.01$). No excess risk of CVD mortality was observed for either supper time of <17:00 or >20:00. These associations did not alter when the supper times of <17:00 and 17:00–20:00 were combined as a reference.

Table 3 shows the results of the stratified analysis by history of hypertension. Among hypertensives, irregular supper time was associated with a higher risk of CVD mortality; the multivariable HR (95% CIs) was 1.32 (1.02–1.70, $P=0.03$). Supper time of >20:00 was not associated with age- and sex-adjusted risk of CVD mortality, but the association reached marginally statistical significance ($P=0.06$) after the multivariable adjustment. A slight strengthening of the association was observed when educational level and occupational status were added to the age- and sex-adjusted models; the HR (95% CI) was 1.37 (0.97–1.93, $P=0.07$).

Among nonhypertensives, irregular supper time but not supper time >20:00 was associated with the higher risk; the multivariable HRs (95% CIs) were 1.26 (1.05–1.51, $P=0.01$) and 0.98 (0.72–1.35, $P=0.92$), respectively. The interaction between the supper time of >20:00 and the history of

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Table 1. Mean values ± standard derivations and proportions of baseline characteristics according to supper time

Supper time	17:00-20:00	＜17:00	＞20:00	Irregular
Demographics				
No. at risk, n	65,890	223	1,968	4,577
Age, years	57.5 ± 10.0	62.7 ± 10.9	51.2 ± 8.7	51.2 ± 8.9
Men, n (%)	26,327 (40.0)	94 (42.2)	1,098 (55.8)	2,685 (58.7)
Social economic status				
College or higher education, n (%)	7,589 (11.5)	14 (6.3)	350 (17.8)	690 (15.1)
Office worker, n (%)	5,437 (8.3)	4 (1.8)	409 (20.8)	876 (19.1)
Married, n (%)	53,324 (80.9)	134 (60.1)	1,666 (84.7)	3,763 (82.2)
Health behaviors and comorbidity				
Current or past smokers, n (%)	21,591 (32.8)	84 (37.7)	918 (46.7)	2,325 (50.8)
Body mass index ≥ 25 kg/m², n (%)	12,598 (19.1)	39 (17.5)	403 (20.5)	1,032 (22.6)
History of hypertension, n (%)	14321 (21.7)	75 (33.6)	282 (14.3)	708 (15.5)
History of diabetes mellitus, n (%)	2,870 (4.4)	16 (7.2)	68 (3.5)	189 (4.1)
Sleeping duration of 5.5-7.4 hours/day, n (%)	33,680 (51.1)	85 (38.1)	1,308 (66.5)	2,929 (64.0)

Table 2. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from cardiovascular disease according to supper time

Supper time	17:00-20:00	＜17:00	＞20:00	Irregular
Total population				
Person-years	1,080,080	3,009	33,362	76,273
No. at risk	65,890	223	1,968	4,577
No. of deaths	4,569	19	72	190
Age- and sex-adjusted HR (95% CI)	Reference	0.99 (0.63-1.55)	1.10 (0.87-1.39)	1.28 (1.11-1.48)
Multivariable HR (95% CI)	Reference	0.94 (0.60-1.48)	1.11 (0.88-1.40)	1.28 (1.11-1.49)
Multivariable HR (95% CI)	Reference		1.11 (0.88-1.40)	1.28 (1.11-1.49)

Multivariable HRs were adjusted for further, body mass index, smoking, history of hypertension, history of diabetes, sleep duration, educational level, occupational status, and marital status.

Table 3. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of risk of mortality from cardiovascular disease according to supper time, stratified by history of hypertension

Supper time	17:00-20:00	＜17:00	＞20:00	Irregular
Hypertensives				
Person-years	213,932	926	4,426	10,568
No. at risk	14,321	75	282	708
No. of deaths	1,849	10	33	63
Age- and sex-adjusted HR (95% CI)	Reference	1.21 (0.65-2.24)	1.35 (0.95-1.90)	1.31 (1.02-1.69)
Multivariable HR (95% CI)	Reference	1.19 (0.64-2.21)	1.39 (0.98-1.96)	1.32 (1.02-1.70)
Multivariable HR (95% CI)	Reference		1.38 (0.98-1.96)	1.32 (1.02-1.70)
Non-hypertensives				
Person-years	866,148	2,083	28,936	65,704
No. at risk	51,569	148	1,686	3,869
No. deaths	2,720	9	39	127
Age- and sex-adjusted HR (95%CI)	Reference	0.82 (0.43-1.58)	0.95 (0.70-1.31)	1.30 (1.09-1.55)
Multivariable HR (95% CI)	Reference	0.75 (0.39-1.45)	0.98 (0.72-1.35)	1.26 (1.05-1.51)
Multivariable HR (95% CI)	Reference		0.98 (0.72-1.35)	1.26 (1.05-1.51)

Multivariable HRs were adjusted for further, body mass index, smoking, history of diabetes, sleep duration, educational level, occupational status, and marital status.
P-interaction of supper time of ＜17:00, ＞20:00 and irregular, with a history of hypertension was 0.42, 0.12, and 0.55, respectively.

Advance Publication Journal of Atherosclerosis and Thrombosis
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Table 4. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of mortality from cardiovascular disease according to supper time, stratified by the combination of history of hypertension and age

Supper time	17:00-20:00	<17:00	>20:00	Irregular
Hypertensives aged < 65 years				
Person-years	137,342	500	3,616	9,234
No. at risk	8,363	32	215	587
No. of deaths	572	3	15	28
Age- and sex-adjusted HR (95% CI)	Reference	1.54 (0.50-4.79)	1.34 (0.80-2.24)	0.93 (0.64-1.37)
Multivariable HR (95% CI)	Reference	1.40 (0.45-4.38)	1.41 (0.84-2.38)	0.95 (0.64-1.39)
Multivariable HR (95% CI)	Reference		1.41 (0.84-2.37)	0.95 (0.64-1.39)
Hypertensives aged ≥ 65 years				
Person-years	76,590	426	810	1,334
No. at risk	5,958	43	67	121
No. of deaths	1,277	7	18	35
Age- and sex-adjusted HR (95% CI)	Reference	1.10 (0.53-2.32)	1.29 (0.81-2.05)	1.80 (1.28-2.51)
Multivariable HR (95% CI)	Reference	1.12 (0.53-2.37)	1.34 (0.84-2.13)	1.80 (1.28-2.52)
Multivariable HR (95% CI)	Reference		1.34 (0.84-2.13)	1.80 (1.28-2.52)
Non-hypertensives aged < 65 years				
Person-years	712,208	1,288	27,488	62,326
No. at risk	40,484	80	1,576	3,597
No. of deaths	1,094	3	25	83
Age- and sex-adjusted HR (95% CI)	Reference	1.77 (0.57-5.51)	0.81 (0.55-1.21)	1.17 (0.93-1.47)
Multivariable HR (95% CI)	Reference	1.52 (0.49-4.74)	0.82 (0.55-1.22)	1.13 (0.90-1.42)
Multivariable HR (95% CI)	Reference		0.82 (0.55-1.22)	1.13 (0.90-1.42)
Non-hypertensives aged ≥ 65 years				
Person-years	153,940	795	1,449	3,378
No. at risk	11,085	68	110	272
No. deaths	1,626	6	14	44
Age- and sex-adjusted HR (95%CI)	Reference	0.64 (0.29-1.42)	1.11 (0.66-1.88)	1.29 (0.96-1.74)
Multivariable HR (95% CI)	Reference	0.60 (0.27-1.35)	1.18 (0.70-2.00)	1.26 (0.93-1.70)
Multivariable HR (95% CI)	Reference		1.18 (0.70-2.00)	1.26 (0.93-1.70)

Multivariable HRs were adjusted for further, body mass index, smoking, history of diabetes, sleep duration, educational level, occupational status and marital status.

P-interaction of supper time of <17:00, >20:00 and irregular with age among hypertensives was 0.89, 0.29 and <0.01, respectively.

hypertension did not reach statistical significance (*P* for interaction =0.12). Again, these associations did not change when the supper times of <17:00 and 17:00–20:00 were combined as a reference.

Table 4 shows the results of the stratified analysis by the combination of history of hypertension and age group. The excess risk of CVD mortality for irregular supper time was evident for older hypertensives but not for younger ones; the multivariable HRs (95% CI) were 1.80 (1.28–2.52, $P<0.01$) and 0.95 (0.64–1.39, $P=0.78$), respectively (*P* for interaction <0.01). The association did not alter when supper times of <17:00 and 17:00–20:00 were combined as a reference.

Discussion

In our prospective population-based cohort study, compared with supper time of 17:00–20:00, irregular supper time was associated with an increased risk of CVD mortality for the total population, either hypertensives or nonhypertensives, particularly hypertensives aged ≥ 65 years. The excess risk of CVD mortality associated with a supper time of >20:00 had marginal statistical significance in the multivariable model.

Potential mechanisms underlying irregular supper times and the risk of CVD mortality, particularly in older hypertensives, should be discussed. For example, meal timing affects circadian rhythms[11, 12] and is associated with oxidative stress[13]. According to a previous study of 542 Japanese women,

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46 women who ate dinner at irregular times tended to have higher oxidative stress markers than 264 women with regular dinner times: urinary levels of 8-isoprostane (median: 150.8 versus 138.0 pg/mg creatinine, P for difference=0.17)[7]. An 18-year cohort study of 392 postmenopausal women showed that the risk of mortality from CVD was 80% (95% CI: 1.1–3.1) higher for the highest versus lowest quartiles of urinary 8-isoprostane levels[14]. Higher oxidative stress induces endothelial dysfunction and may contribute to the development of atherosclerosis by directly damaging the vascular endothelium or by inducing cell proliferation, hypertrophy, or apoptosis via intracellular signaling pathways[15]. The oxidative stress leads to inflammation, plaque development, and instability, resulting in plaque rupture[16]. The excess risk of CVD mortality for irregular supper time among older hypertensives may be attributed to persistent hypertension accelerating aging-related changes in vascular functions and structure such as endothelial dysfunction, arterial stiffness, and atherosclerosis[8, 17-19] or arteriolosclerosis[20]. In addition, both irregular and late supper times likely cause overweight and obesity[21, 22], which is associated with an increased risk of CVD mortality when obesity is accompanied by hypertension[23].

Notably, the excess risk of CVD mortality associated with a supper time of >20:00 was slightly higher in the multivariable model than in the age- and sex-adjusted models because socioeconomic status such as education level and occupational status was higher in people with a supper time of >20:00 than in those with a supper time of 17:00–20:00. Further studies are required to explore the underlying mechanisms.

Strengths and Limitations

The strength of this study was that it was a prospective cohort with a nationwide population in Japan, which facilitated the analysis of the association between supper time and the risk of CVD mortality in patients with and without hypertension. However, this study has some limitations. First, this study used mortality data as an endpoint. Therefore, there might have been some misclassification between the diagnoses of CVD deaths. However, the validity of the diagnosis on death certificates since the 1980s has been confirmed[24, 25]. Second, the number of CVD deaths was small and did not satisfy statistical power in stratified analysis, particularly at the supper time of <17:00, which needed to be interpreted carefully. However, when the supper times of <17:00 and 17:00–20:00 were combined as a reference, the result did not change. Third, the impact of unmeasured and residual confounders such as bedtime, other clinical information, and social backgrounds remained to be examined. Finally, a history of hypertension was defined using a self-reported questionnaire. However, a subsample of 20,389 individuals showed a good correlation between a history of hypertension and the prevalence of hypertension, estimated by blood pressure levels and anti-hypertensive medication use at a health checkup assessment.

Conclusion

Irregular supper time was associated with an increased risk of CVD mortality for the total population, either hypertensives or nonhypertensives, especially older hypertensives. Supper timing could be a surrogate marker for CVD risk.

Authors' Contributions

TI and RS designed the study. TI drafted the manuscript. TI performed statistical analyses. RS and HIs supervised the preparation of the manuscript. KS, EE, MI, JD, HIm, and AT critically revised the manuscript for important intellectual content. All authors were involved in data interpretation. HIs, and AT obtained funding and provided administrative support. AT was the principal investigator in the JACC study. HIs and AT designed the survey and collected data. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Disclosures

The authors have no conflicts of interest to declare.

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Supplemental Table 1. Mean values ± standard derivation and proportions of baseline characteristics according to supper time among participants with hypertension and without hypertension

Supper time	17:00-20:00	<17:00	>20:00	Irregular
Hypertensives				
Demographics				
No. at risk, n	14,321	75	282	708
Age, years	62.3 ± 8.8	65.5 ± 8.3	57.1 ± 9.8	56.0 ± 9.3
Men, n (%)	5,489 (38.3)	29 (38.7)	134 (47.5)	376 (53.1)
Social economic status				
College or higher education, n (%)	1,396 (9.8)	4 (5.3)	41 (14.5)	89 (12.6)
Office worker, n (%)	884 (6.2)	0 (0.0)	45 (16.0)	110 (15.5)
Married, n (%)	10,799 (75.4)	42 (56.0)	220 (78.0)	564 (79.7)
Health behaviors and comorbidity				
Current or past smokers, n (%)	4,582 (32.0)	25 (33.3)	126 (44.7)	334 (47.2)
Body mass index ≥ 25 kg/m^2, n (%)	3,872 (27.0)	16 (21.3)	80 (28.4)	239 (33.8)
History of diabetes mellitus, n (%)	1,144 (8.0)	12 (16.0)	24 (8.5)	61 (8.6)
Sleeping duration of 5.5-7.4 hours/day, n (%)	6,534 (45.6)	31 (41.3)	190 (67.4)	430 (60.7)
Non-hypertensives				
Demographics				
No. at risk, n	51,569	148	1,686	3,869
Age, years	56.2 ± 10.0	61.2 ± 11.7	50.2 ± 8.1	50.3 ± 8.5
Men, n (%)	20,838 (40.4)	65 (43.9)	964 (57.2)	2,309 (59.7)
Social economic status				
College or higher education, n (%)	6,193 (12.0)	10 (6.8)	309 (18.3)	601 (15.5)
Office worker, n (%)	4,553 (8.8)	4 (2.7)	364 (21.6)	766 (19.8)
Married, n (%)	42,525 (82.5)	92 (62.2)	1,446 (85.8)	3,199 (82.7)
Health behaviors and comorbidity				
Current or past smokers, n (%)	17,009 (33.0)	59 (39.9)	792 (47.0)	1,991 (51.5)
Body mass index ≥ 25 kg/m^2, n (%)	8,726 (16.9)	23 (15.5)	323 (19.2)	793 (20.5)
History of diabetes mellitus, n (%)	1,726 (3.4)	4 (2.7)	44 (2.6)	128 (3.3)
Sleeping duration of 5.5-7.4 hours/day, n (%)	27,146 (52.6)	54 (36.5)	1,118 (66.3)	2,499 (64.6)

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